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Ionic Liquids : A New Trend in Drug Synthesis Using Green Chemistry

Dr. Amit Gosar[1], Dr. Sayyed Hussain[2], Tabrez Shaikh[3*], Amit Joglekar[3]
[1]*Chief Scientist, Indoco Remedies Ltd, ARD department, Navimumbai, Maharashtra, India*
[2]*Associate Professor, Sir Sayyed College, Department of Chemistry, Aurangabad, Maharashtra, India*
[3]*Principal Scientist, Indoco Remedies Ltd, ARD department, Navimumbai, Maharashtra, India*
***Email:** tabrezs@indoco.com
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Abstract

Environmental pollution is majorly caused by the chemical and pharmaceutical industries which have increased multifold time in the last several decades. It is the responsibility of science to design the process which will generate the less hazardous chemicals and much environmentally friendly waste. Ionic liquid finds a source of hope in reducing the organic solvent waste in coming years. These Ionic liquids may replace the organic solvents which are hazardous, toxic and non-environmentally friendly used in the synthesis of chemical compounds. This review article describes the Introduction to Ionic liquids, their types and classification, the advantages of their use in replacement of organic solvent in the synthesis of chemicals compounds and drug substances.

Keywords: *Ionic liquids, Synthesis, properties, application*

INTRODUCTION AND DEFINITION

Waste is any unwanted material in all the forms that can cause harm by being inhaled, swallowed, and absorbed through the skin or damage the environmental life cycle. The major contribution to environmental waste is organic chemicals which come from various industries. Pharmaceutical industries comprise the largest source of organic pollutants among all the industries while organic solvent waste is major waste which is expelled by these industries. As the world is facing serious environmental challenges, many environmental protection agencies suggested that green chemistry should be used by chemical and pharmaceutical industries in order to reduce toxic, undesired waste, and environmental waste. If the processes can be implemented right, green chemistry can afford to reduce waste product and decrease the resource consumption. Presently the organic waste is the major waste generated in all the manufacturing industries which compromise upto 35 % (Figure-1) of total waste [1-2]

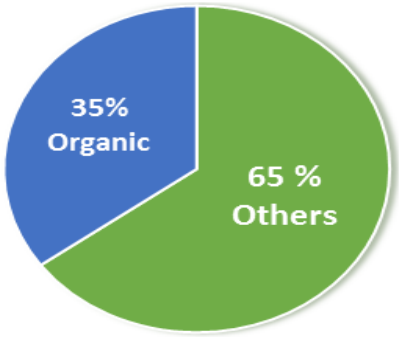

Figure 1: *Waste pie chart*

Looking at the Michigan hierarchy waste management chart (Figure-2), avoiding and reducing the amount of chemical waste generated is more preferable and cost-effective when compared to adopting waste management practices such as reducing, recycling, recovering and disposing to the environment. Considering this, the use of Ionic liquid in the manufacturing of pharmaceutical was incorporated in the 1990s in replace of conventional organic solvents. Thus ionic liquids began to be considered as environmentally benign compared to organic solvent [3].

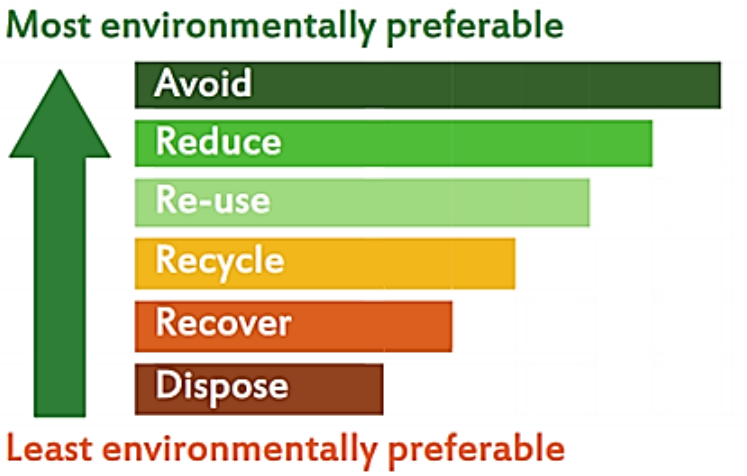

Figure 2: *Michigan hierarchy of waste management*

Ionic liquids

What are ionic liquids (ILs)? The very answer is in this question only. Thus Ionic liquids are liquids that consist ion of an organic cation and organic or inorganic polyatomic anion (figure-3). Since there are many known and potential cations and anions, the potential number of ionic liquids compared to organic solvents is very huge. Thus discovering a new ionic liquid is easy. The ion liquid discovery is attributed to Paul Walden, who made the ionic liquid and studied their physical-chemical properties. These ionic liquids have a very vast application, but for our subject, it is limited to its use in synthesis in replace of organic solvents which are hazardous, toxic and not environmental friendly [4].

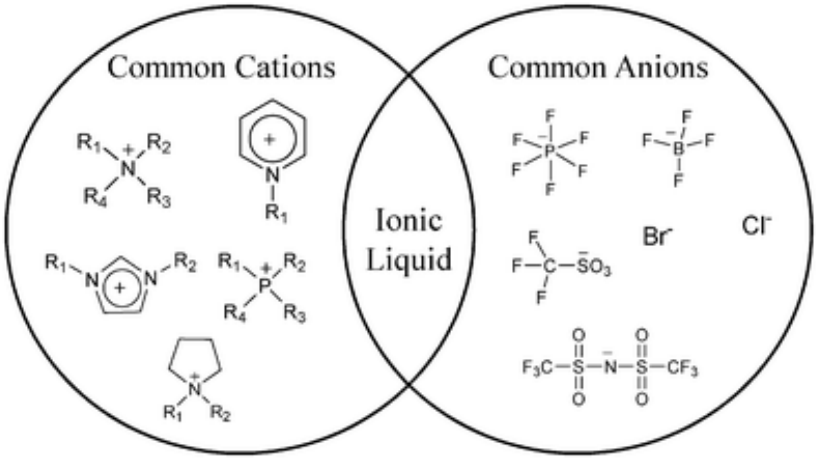

Figure 3: *Ionic liquid cation and anions*

Cations

The ionic liquid cation generally consists of an organic structure with positively charged. The most common cations in ionic liquids are nitrogen or phosphorous containing organic ions. Physical and chemical properties of ionic liquids are influenced by the cation present in them.

Anions

The ionic liquid anion generally consists of weakly basic organic or inorganic compounds which are negatively charged. The most common anion in ionic liquids are acetate, nitrate, borate or sulphate ions. Some examples of cation and anion present in ionic liquids are given in Table-1.

Table 1: *Cation and anions of Ionic liquids*

Cations	**Anions**
Alkylammonium	Tetrafluroborate
N, N-dialkylimidazolium	Acetate
N-alkylpyridium	Nitrate
Alkylphosphonium	hexafluorphosphate
Pyrazolium	Methylsulfate
Oxazolium	Trifluoracetate
Triazolium	Chloride, bromide and iodide
Thiazolium	Hexafluroantimonate

Properties of ionic liquids

Properties of Ionic liquid such as melting point, viscosity, and solubility of materials depends on the substituents on the organic component and by the counterion. Their physical and chemical properties can be adjusted by the variation of ions. The fine adjustment of properties is possible by the variation of the length and branching of the alkyl groups incorporated into the cation. Many ionic liquids have even been developed for specific synthetic problems. For this reason, ionic liquids have been termed "designer solvents" [5].

Table 2: *Properties of Ionic liquids*

Properties	Possible Commercialization
Excellent Thermal Stability	No Volatility
	Negligible Vapor Pressure
	Liquid in a Wider Range of Temperature
High Ion Density	High Ion Transport
	High Polarity
High Heat Capacity	Heat Transport
Low Viscosity	Solvent, Electrolyte
	Reacting Stimulation
Diverse Organic Ions	Myriad Combinations of Anions and Cations
	Possible Structural Design
	Possible Functional Production

Melting point

As Ionic liquids are used in replace of organic solvents which are liquid at room temperature, hence their melting point should be that of water in order to work with them at room temperature. The magnitude of the melting point is found related to the structure and composition of ionic liquids. Hence, selecting cation and anion for ionic liquid determines the melting point of ionic liquids.

Density

Cation and anion present in ionic liquid decide its density. Practically the density observed of ionic liquids are between 1.0 to 1.35 gcm-3. The bulkiness of organic anion present in ionic liquid determines the density of ionic liquids. Density tends to decrease with an increase in bulkiness.

Thermal stability

Solvent use in the synthesis should be thermally stable at all the working temperature. Ionic liquids are found to be much stable at or above 400°C when compared to organic solvents. Anion part of ionic liquid contributes greatly toward the thermostability of liquids as compared to cations. Hydrophilicity of anion decrease the thermal stability of ionic liquids.

Viscosity

Ionic liquid should have mid-viscosity when compared to organic solvents. It should be neither highly viscous nor low viscous which make unable to handle it or hard to mix with the starting material for synthesis.

Volatility

One major problem with organic solvent is that they are highly volatile, which make them to reproduce the process which can

be overcome by the use of Ionic liquids, as most of these are non-volatile hence repeatability of the process is very high.

Synthesis of ionic liquids

The synthesis of ionic liquids can be described in two steps.

(1) The Formation of the Desired Cation. The desired cation can be synthesized either by the protonation of the amine by an acid or through quaternization reactions of the amine with a haloalkane and heating the mixture.

(2) Anion Exchange. Anion exchange reactions can be carried out by treatment of halide salts with Lewis acids to form Lewis acid-based ionic liquids or by anion metathesis.

As ionic liquid is formed by combination of two or more ions, Due to combination of two or more ion there are many possiblity of Ionic liquids can be synthesied and designed [6].

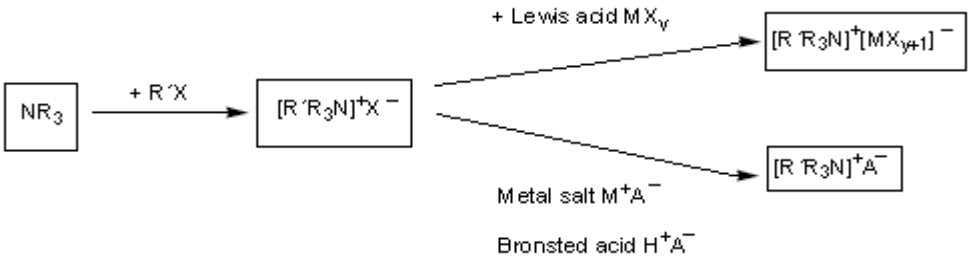

Figure 4: *Synthesis of ionic liquid*

Advantages of ionic liquid

Ionic liquids (ILs) have very good properties as a reaction medium for chemical reactions, generally, they are non-volatile, non-flammable, have low toxicity and good solubility for many organic and inorganic materials. QSAR toxicity assessment of their structure confirms the nontoxic nature of most of the ionic liquids. They can easily adapt the process scale without any major changes in the process.

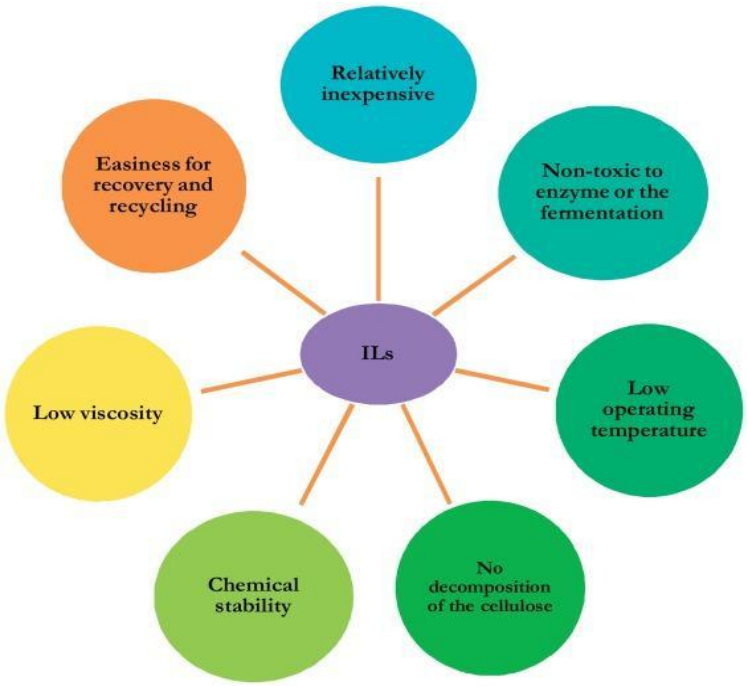

Figure 5: *Advantages of Ionic liquids*

Application of ionic liquid

Ionic liquids find very vast and versatile application as compared to organic solvents (Figure-6 and 7). Some of these applications are illustrated and discuss as below [7-8].

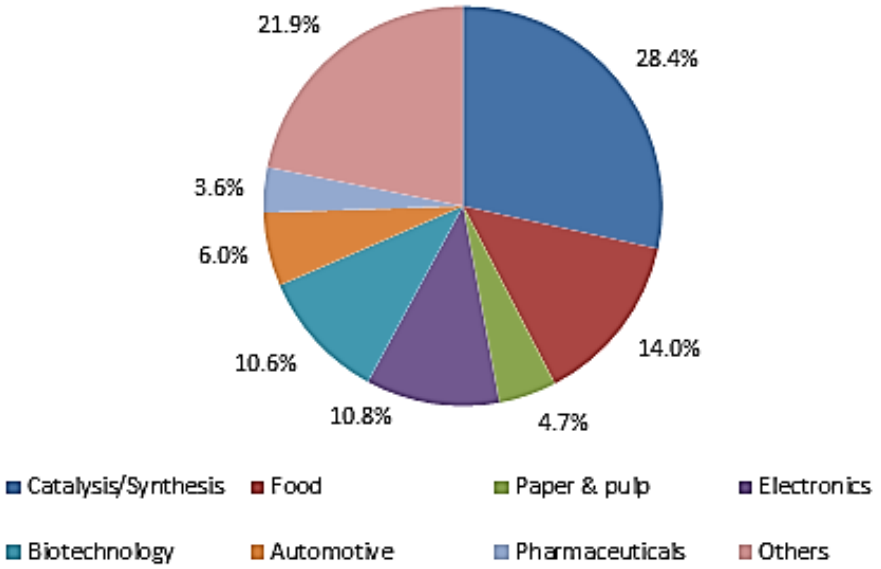

Figure 6: *Market of Ionic liquids*

Drug synthesis

Organic volatile solvent are not very environment friendly and lead to to considerable waste druing drug synthesis. These volatile organic solvent are also not cost effictively reusable. Thus safer alternative to these solvent are ionic liquid which can be safely recovered and reused. Ionic liquids are used as solvent in synthsis of raw materials, intermediate and drug substances. Some of chemical reaction where ionic liquid can be used are Diels–Alder reaction, Friedel–Crafts reaction, Esterification reaction, displacement reaction with cyanide, reduction of aldehydes and ketone, beckmann rearrangement etc.

Polymerisation

As ionic liquid provide the strong ionic media, it helps in chain propogation hence while increase in chain group in cationic part leads to chain termination due to high viscosity. Hence changing the structure of the ionic liquid, required molecular weight polymer can be synthesized. Hence it find application in poymer industries.

Solvent extraction

Ionic liquids have been extensively used for the liquid-liquid extraction of metals, small organic molecules, hydrocarbons, large biomolecules such as proteins and DNA. This wide applicability derives from the possibility of ad hoc design of ionic liquid used as extractant. In this way, the selectivity and efficiency can be modulated from the specific application as well as the solubility and miscibility between the extractant and the sample matrix.

Separation techniques

Ionic liquids are also been used in seperation techniqes such as Thin layer chromatography and electrophoresis. It improve the electrophoretic separation in non aqueous capillary electrophoresis as their use in the conventional mode is hindered by their high viscosity and conductivity. Ionic liquids have also been covalently bonded to the inner surface of the fused silica capillary to reduce the analytes adsorption and reverse the electrosmotic flow. Biomolecules such as DNA, proteins, drugs and inorganic cations have been successfully separated

using capillaries modified with Ionic liquids. The reusability and the reproducibility improvement have been reported as additional advantages.

Enviornment

The use of ionic liquids in carbon capture is a potential application of ionic liquids as absorbents for use in carbon capture . The urgency of climate change has spurred research into their use in energy-related applications such as carbon capture and storage. Various ionic liquids are used for this purpose.

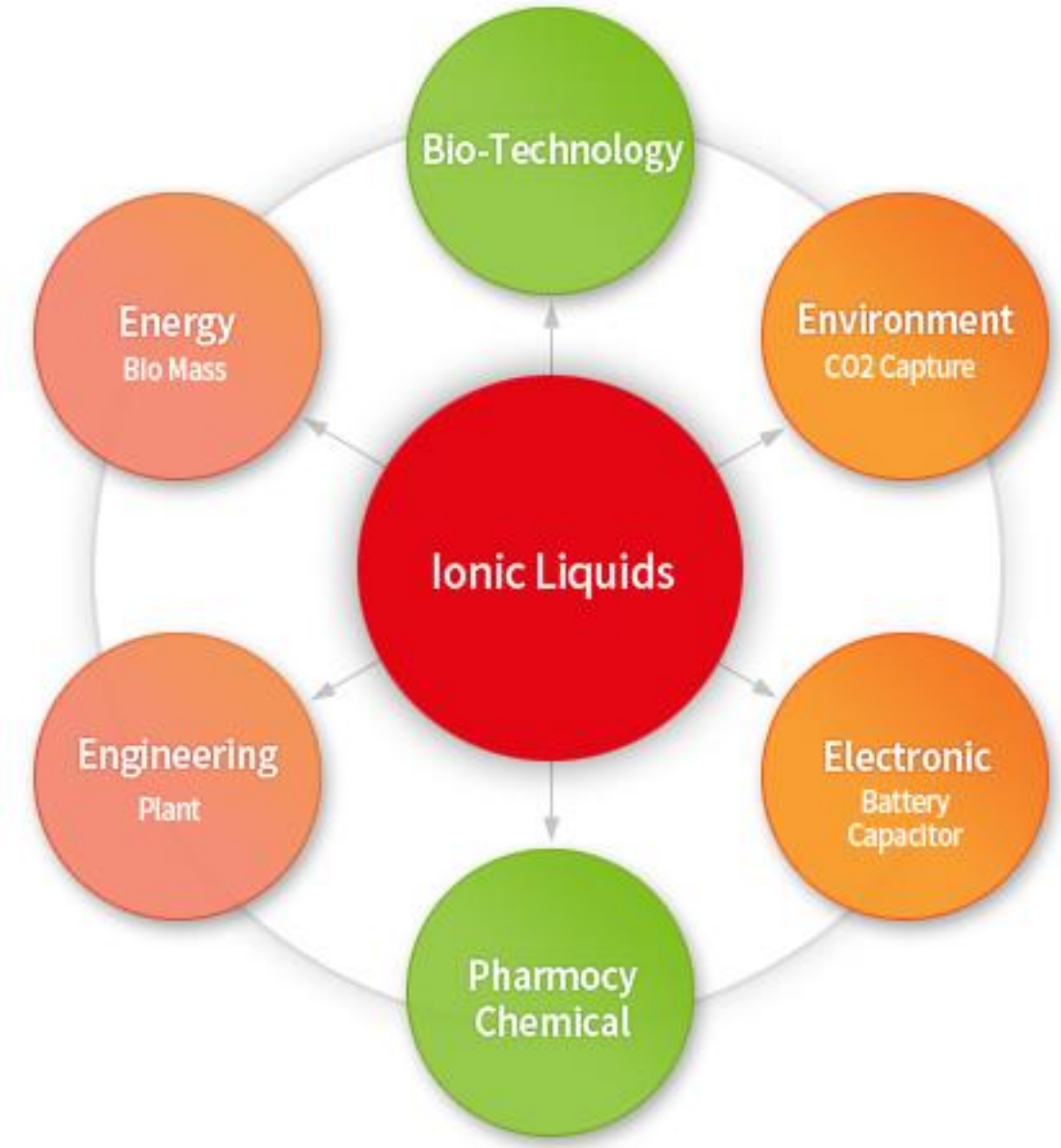

Figure 7: *Market of Ionic liquids*

CONCLUSION

The need for green chemistry will increase in the future. Hence replacement or limiting the use of solvents for chemicals processing will remain a dynamic area for research. Ionic liquid dues to its properties such as low volatility, non-flammability, low melting point, high thermal stability, controlled miscibility, recyclability and no toxicity, finds a hope for the green

chemistry. Due to high selectivity and activity of ionic liquids, there is growing interest in developing applications for them in a wide range of synthetic reactions. Further, its application is found in environmental chemistry, engineering, biotechnology and electronic industries. Ionic liquids have all potential to replace conventional solvent in both laboratories and industry.

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